

# 1-Propanephosphonic Acid Cyclic Anhydride (T3P) as an Efficient Promoter for the Lossen Rearrangement: Application to the Synthesis of Urea and Carbamate Derivatives

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**Abstract:** The synthesis of hydroxamic acids starting from carboxylic acids employing 1-propanephosphonic acid cyclic anhydride (T3P) activation is described. Application of ultrasonication accelerates this conversion. Further, the T3P has also been employed to activate the hydroxamates, leading to isocyanates via the Lossen rearrangement. The isocyanates were trapped with suitable nucleophiles to afford the corresponding ureas and carbamates.

**Key words:** T3P, hydroxamic acids, Lossen rearrangement, isocyanates

Functional group transformation has acquired a significant place in organic chemistry. Among a plethora of intermediates described, isocyanates<sup>1</sup> have been one of the outstanding discoveries due to their vast application in synthetic as well as biological studies.<sup>2,3</sup> Consequently, there has been significant interest in the development of new and simpler protocols for the preparation of isocyanates.

Classical Curtius rearrangement of acyl azides is a well-known reaction for the synthesis of isocyanates.<sup>4</sup> Activated carboxylic acids in the form of acid chlorides or mixed anhydrides are subjected to azidolysis or the carboxylic acids are directly converted into acyl azides employing azide-transfer reagents and then the acyl azides are rearranged under thermal conditions.<sup>5–9</sup> Although decent yields are obtained, multistep sequences, the cost of some of the reagents and the potentially explosive nature of acid azides limit this method mainly to bench-scale preparations. Isocyanates can also be accessed via the Hofmann rearrangement, which involves oxidant-mediated conversion of an amide into isocyanate.<sup>10</sup> This protocol requires a large excess of base and hence is not compatible with amino acid chemistry considering the epimerization problems.

The Lossen rearrangement (LR), which describes the transformation of activated hydroxamic acids into isocyanates, is a valid alternative for an easy access to isocyanates.<sup>4</sup> Reagents such as *p*-toluenesulfonyl chloride,<sup>11</sup> cyanuric chloride,<sup>12</sup> 1,1'-carbonyldiimidazole,<sup>13</sup> acylating agents,<sup>14</sup> *N,N'*-dicyclohexylcarbodiimide<sup>15</sup> and *N*-benzyl-

*N'*-(3-dimethylaminopropyl)carbodiimide<sup>16</sup> have been utilized to bring about this transformation. Recently, we reported a facile LR of *N*<sup>α</sup>-urethane-protected amino acid hydroxamates into isocyanates employing *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride.<sup>17</sup> The LR of preactivated hydroxamic acids is also known.<sup>18a</sup> A common drawback posed by several methods, however, is the accumulation of isocyanate before the complete activation of hydroxamic acid leading to self-condensed byproduct.<sup>18b</sup> Such complexities of existing protocols warrant a facile activation of hydroxamic acids leading to isocyanates.

1-Propanephosphonic acid cyclic anhydride (T3P) is one of the economic and efficient coupling agents and is also a water scavenger. Advantages such as high-yielding reactions, broad functional group tolerance, low epimerization and easy workup procedures make the reagent meritorious over several contemporaries. The byproducts are water soluble and eliminate the need for chromatographic purification. Applications of T3P in the synthesis of peptides,<sup>19</sup> Weinreb amides and nitriles are well documented.<sup>20–24</sup> We reasoned that T3P, being a carboxy activator, can be employed for the preparation of hydroxamates from the corresponding acids and, being a dehydrating agent, could be a suitable promoter for the LR via O-activation. To the best of our knowledge, except for a couple of examples of the LR of benzoic acid hydroxamates to Boc/Z-protected anilines,<sup>25</sup> a meticulous study on the T3P-mediated LR for the conversion of hydroxamates into isocyanates is yet to be reported. We herein describe the T3P-promoted LR of hydroxamates derived from aromatic acids, as well as *N*<sup>α</sup>-protected amino acids, into isocyanates and conversion of the latter into urea, carbamate and thiocarbamate derivatives (Scheme 1).

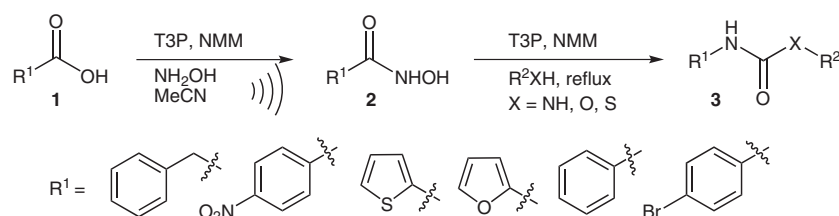
Hydroxamic acids are valuable compounds for their pharmacokinetic merits as well as their synthetic utility.<sup>26,27</sup> Reaction of hydroxylamine with activated carboxylic acid derivatives (such as acid chlorides, mixed anhydrides, oxazolidinones, esters)<sup>28,29</sup> is employed for their preparation. They have also been obtained starting from aldehydes by employing the Angeli–Riminis reaction on a solid support.<sup>30a</sup> Hypervalent iodine(III) mediated oxidation of aldoximes has also been demonstrated.<sup>30b</sup> T3P is a superior, traceless and environmentally benign promoter for *N*-acylation. Appendino's group reported a 12-hour reaction

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Scheme 1 Synthesis of hydroxamates and urea/carbamate derivatives

Table 1 Hydroxamates **2** and Urea/Carbamate Derivatives **3**

Entry	R <sup>1</sup> CONHOH <b>2</b> , Yield (%)	HRMS [M + Na] <sup>+</sup> obsd (calcd)	Mp (°C)	R <sup>1</sup> NHCOXR <sup>2</sup> <b>3</b> , Yield (%)	HRMS [M + Na] <sup>+</sup> obsd (calcd)	Mp (°C)
1	 <b>2a</b> , 88	174.0535 (174.0531)	waxy solid <sup>30a</sup>	 <b>3a</b> , 85	283.0619 (283.0614) 272.1091 (272.1085)	gum <sup>38a</sup> gum
2	 <b>2b</b> , 86	205.01 <sup>a</sup> (205.02)	135–137	 <b>3b</b> , 75  <b>3c</b> , 86	294.0849 (294.0855) 233.07 <sup>a</sup> (233.05)	187–188 (188) <sup>38a</sup> 92–93 (93) <sup>38a</sup>
3	 <b>2c</b> , 85	165.9944 (165.9939)	122–123 (122–123) <sup>30a</sup>	 <b>3d</b> , 75  <b>3e</b> , 89	318.9511 (318.9517)	244 (245) <sup>38a</sup>
4	 <b>2d</b> , 89	128.0341 <sup>b</sup> (128.0348)	120–121	 <b>3f</b> , 91	219.0751 (219.0746)	176
5	 <b>2e</b> , 85	160.0368 (160.0374)	125–127 (126–127) <sup>30a</sup>	 <b>3g</b> , 84	250.09 <sup>a</sup> (250.08)	188
6	 <b>2f</b> , 83	237.9486 (237.9480)	184–185 (184–185) <sup>30b</sup>	 <b>3h</b> , 79	327.9941 (327.9949)	167

<sup>a</sup> ESI-MS.<sup>b</sup> [M + H]<sup>+</sup>.

protocol for the T3P-mediated synthesis of hydroxamic acids at room temperature.<sup>31</sup> With our previous experience and published work on ultrasound-accelerated reactions,<sup>32</sup> we reasoned that ultrasonic waves may hasten this process and render the formation of hydroxamic acids from the corresponding carboxylic acids in a shorter duration of time. Practically, this was the case and we could reduce the reaction time from 12 hours to 60 minutes under ultrasonication. Initially, a solution of *p*-nitrobenzoic acid and an equimolar quantity of T3P in acetonitrile in the presence of *N*-methylmorpholine (NMM) was stirred at 0 °C to facilitate activation. After 15 minutes, hydroxylamine was added and the reaction was run under ultrasonication for another 30 minutes to allow for the completion of the reaction (Scheme 1). A simple workup led to the isolation of *N*-hydroxy-4-nitrobenzamide (**2b**) in good yield (86%); a single recrystallization from tetrahydrofuran–hexane gave analytically pure sample as a crystalline solid (Table 1, entry 2). Five more hydroxamic acids, **2a**, **2c–f**, were also made in a similar way, starting from phenylacetic acid, 2-thiophenic acid, 2-furoic acid, benzoic acid and *p*-bromobenzoic acid (Table 1, entries 1, 3–6).

Further, the protocol was extended to the preparation of a series of *N*<sup>α</sup>-protected amino acid hydroxamates **4** (Table 2). Several procedures have been reported<sup>33</sup> for such compounds, including a one-pot preparation employing cyanuric chloride in the presence of 4-(dimethylamino)pyridine.<sup>34</sup> Mordini and co-workers demonstrated the microwave-assisted transformation of *N*-protected amino acid esters into the corresponding hydroxamic acids.<sup>35</sup> Previously, we have reported the magnesium oxide mediated synthesis of *N*<sup>α</sup>-Fmoc-protected amino acid hydroxamates employing the corresponding acid chlo-

rides;<sup>36</sup> however, due to the instability of the acid chlorides, the protocol could not be extended to *N*-Boc or *Z*-protected amino acids. To develop a common and mild protocol for the synthesis of hydroxamates compatible with all three of the common urethane-protected amino acids (Fmoc, Boc, *Z*), we began our study with a *N*<sup>α</sup>-Boc-protected amino acid. Thus, a solution of *N*<sup>α</sup>-Boc-Phe-OH in acetonitrile in the presence of NMM was treated with T3P at 0 °C for 15 minutes. After the addition of hydroxylamine, the mixture was subjected to ultrasonication. Satisfactorily, the reaction proceeded smoothly and was complete in about 90 minutes, to yield *N*<sup>α</sup>-Boc-Phe-NHOH (**4h**) in 89% yield. Similarly, Fmoc- and *Z*-protected α-amino acids were also converted into their corresponding hydroxamates **4** (Table 2).

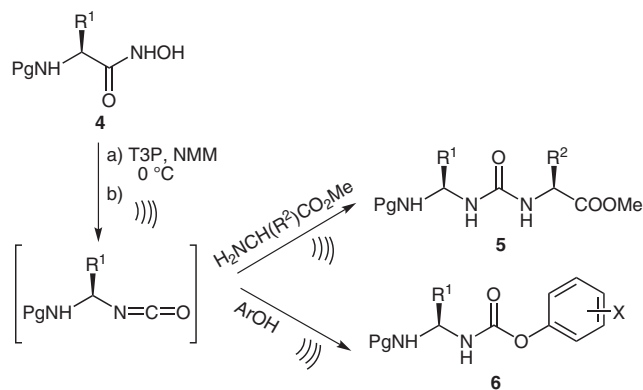
In the next stage, the LR of the hydroxamates, mediated by T3P, was carried out. A chilled solution of hydroxamate **2b** and T3P in tetrahydrofuran in the presence of NMM was stirred for about 30 minutes. After the completion of O-activation of the hydroxamate (TLC analysis), the mixture was refluxed for 1.5 hours. The IR spectrum of the reaction mixture showed a strong peak at 2240 cm<sup>−1</sup>, corresponding to the isocyanate. The O-activation of hydroxamic acids takes a longer time than that required for carboxy activation during the preparation of hydroxamates, and an excess of T3P is required to drive the reaction towards completion. After confirming the formation of isocyanates, our next objective was to trap them with nucleophiles such as amines, alcohols and thiols. Towards this end, typically, after stirring a solution of hydroxamate **2b** along with T3P and NMM in tetrahydrofuran at 0 °C for 30 minutes, the reaction mixture was refluxed in the presence of a nucleophile such as *p*-methylaniline. After completion of the reaction (3 h), a simple workup led to

**Table 2** *N*-Urethane-Protected Amino Acid Hydroxamates **4**

Hydroxamate <b>4</b>	PG-Xaa-NHOH		Reaction time (min)	Yield (%)	Mp (°C)
	PG	Xaa			
<b>4a</b>	Fmoc	Ala	90	97	128 (128) <sup>36</sup>
<b>4b</b>	Fmoc	Phe	80	93	151–152 (150–152) <sup>34</sup>
<b>4c</b>	Fmoc	Glu( <i>Or</i> -Bu)	85	95	132–133 (131–133) <sup>17</sup>
<b>4d</b>	Fmoc	Ser(OBn)	110	93	163–164 (164) <sup>36</sup>
<b>4e</b>	Fmoc	Phg	80	84	132–133 (132) <sup>36</sup>
<b>4f</b>	<i>Z</i>	Ala	90	91	oil
<b>4g</b>	<i>Z</i>	Phg	90	92	160 (159–161) <sup>17</sup>
<b>4h</b>	Boc	Phe	90	89	oil
<b>4i</b>	Boc	Glu(OBn)	110	79	81–82 (82–83) <sup>34</sup>

the isolation of urea **3c** in 86% yield (Table 1, entry 2). The generality of this reaction was confirmed by the synthesis of ureas **3a**, **3e**, **3f**, carbamates **3d**, **3g**, **3h**, and thiocarbamate **3b** (see Scheme 1 and Table 1).

Finally, the utility of this protocol for the preparation of peptidomimetics was studied. To a chilled solution of *N*<sup>α</sup>-Boc-Phe-NHOH (**4h**) in tetrahydrofuran, T3P and NMM were added, and the mixture was stirred for 30 minutes. Then, after adding H<sub>2</sub>N-Val-OMe (obtained by deprotonation of the corresponding hydrochloride salt using Zn dust<sup>37</sup>), the mixture was refluxed for two hours to obtain the ureidopeptide, albeit in low yield. The not-so-encouraging result obtained using the thermal method led us to test the feasibility of this transformation under ultrasonication. To our delight, when the reaction mixture, after the O-activation step, was subjected to ultrasonication, the activated hydroxamic acid underwent the LR and the isocyanate formed in situ reacted with the amine to afford urea **5c** in a shorter duration (an hour) in good yield (85%) (Scheme 2 and Table 3). A few Boc- and Z-protected α-amino acid hydroxamates were subjected to the LR and the corresponding ureas **5c–e** were isolated as analytically pure products (Table 3). Fmoc-Protected ureidopeptides precipitated as solids from the reaction mixture and a single recrystallization step led to crystalline products (**5a** and **5b**). The protocol was further extended to the preparation of a few active carbamates **6a–c** derived from *N*<sup>α</sup>-protected amino acids by trapping the intermediate isocyanates with substituted phenols (Scheme 2 and Table 3). All products were isolated and characterized by NMR and mass spectroscopy.



**Scheme 2** Synthesis of ureidopeptides **5** and carbamates **6** by the LR of hydroxamates **4**

The protocol was revisited to check whether the methodology demonstrated here is free from racemization. A set of epimeric ureidopeptides, *N*<sup>α</sup>-Fmoc-Phg<sup>U</sup>-L-Ala-OMe (**5f**) and *N*<sup>α</sup>-Fmoc-Phg<sup>U</sup>-D-Ala-OMe (**5g**), were prepared starting from racemization-prone *N*<sup>α</sup>-Fmoc-Phg-OH and their <sup>1</sup>H NMR spectra were examined for the methyl group resonance of the alanyl residue. Distinct doublets were observed at δ = 1.28 and 1.30 ppm for **5f** and at δ = 1.29 and 1.32 ppm for **5g**. This clearly indicates the presence of a single diastereomer in each sample. This, in turn,

**Table 3** Ureidopeptides **5** and Active Carbamates **6**

Urea <b>5</b> /Carbamate <b>6</b>	Yield (%)	Mp (°C)
<b>5a</b> 	96	180 (181) <sup>38a</sup>
<b>5b</b> 	84	140–141 (140) <sup>5a</sup>
<b>5c</b> 	85	138–139
<b>5d</b> 	79	139
<b>5e</b> 	89	142–143 (142–144) <sup>38a</sup>
<b>6a</b> 	91	142
<b>6b</b> 	85	117–118 (117) <sup>38c</sup>
<b>6c</b> 	89	170–171 (171) <sup>38b</sup>

suggests that *N*<sup>α</sup>-Fmoc-Phg-NHOH (**4e**) is epimerically pure, and thus also the urea derivatives prepared from it via the LR to the extent detectable by NMR analysis.

In summary, a facile conversion of aromatic acids, as well as *N*-protected amino acids, into hydroxamates under ultrasonication using T3P as carboxy activator is described. Further, the T3P was employed to mediate the Lossen rearrangement of these hydroxamates. The generated isocyanates were utilized to synthesize urea, carbamate and thiocarbamate derivatives.

All solvents were distilled prior to use and reagents were used as received from Sigma-Aldrich. Melting points were determined on a Buchi model 150 melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Nicolet Impact model 400D FT-IR spectrometer (KBr pellets,  $3\text{ cm}^{-1}$  resolution).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AMX 300-MHz spectrometer. High-resolution mass spectra were recorded on a Micro-mass Q-TOF mass spectrometer.

### Hydroxamic Acids 2; General Procedure

To a chilled ( $0\text{ }^\circ\text{C}$ ) soln of an aromatic acid or a N-protected amino acid (1 mmol) and NMM (0.12 mL, 1.1 mmol) in MeCN (10 mL) was added 50% T3P in EtOAc (0.71 mL, 1.2 mmol). The reaction mixture was stirred at the same temperature for 15 min and then subjected to ultrasonication after the addition of  $\text{NH}_2\text{OH}$  (83 mg, 1.2 mmol; obtained by neutralization of the corresponding hydrochloride salt with NMM) until the reaction was completed. The mixture was diluted with EtOAc (15 mL), and washed with  $\text{H}_2\text{O}$  and brine. The organic phase was dried (anhyd  $\text{Na}_2\text{SO}_4$ ), the solvent was evaporated under reduced pressure, and the residue was recrystallized (THF–hexane).

### N-Hydroxy-4-nitrobenzamide (2b)

Yield: 157 mg (86%); white solid; mp  $135\text{--}137\text{ }^\circ\text{C}$ ;  $R_f = 0.35$  ( $\text{CHCl}_3\text{--MeOH}$ , 9:1).

IR (KBr):  $1642\text{ cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 7.72$  (d,  $J = 5.4\text{ Hz}$ , 2 H), 7.91 (d,  $J = 5.4\text{ Hz}$ , 2 H), 8.57 (s, 1 H), 10.58 (s, 1 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 122.8$ , 128.1, 139.8, 146.8, 166.8.

ESI-MS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_7\text{H}_6\text{N}_2\text{O}_4$ : 205.02; found: 205.01.

Anal. Calcd for  $\text{C}_7\text{H}_6\text{N}_2\text{O}_4$ : C, 46.16; H, 3.32; N, 15.38. Found: C, 46.20; H, 3.28; N, 15.47.

### N-Hydroxyfuran-2-carboxamide (2d)

Yield: 113 mg (89%); white solid; mp  $120\text{--}121\text{ }^\circ\text{C}$  (Lit.<sup>28c</sup>  $119\text{--}122\text{ }^\circ\text{C}$ );  $R_f = 0.40$  ( $\text{CHCl}_3\text{--MeOH}$ , 9:1).

IR (KBr):  $1641\text{ cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 6.80$  (m, 1 H), 7.21 (d,  $J = 6.0\text{ Hz}$ , 1 H), 7.23 (d,  $J = 6.0\text{ Hz}$ , 1 H), 8.89 (s, 1 H), 10.89 (br, 1 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 118.0$ , 121.5, 146.3, 148.8, 172.9.

HRMS:  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_5\text{H}_5\text{NO}_3$ : 128.0348; found: 128.0341.

Anal. Calcd for  $\text{C}_5\text{H}_5\text{NO}_3$ : C, 47.25; H, 3.97; N, 11.02. Found: C, 47.32; H, 3.97; N, 11.09.

### Organic Ureas/Carbamates 3; General Procedure

To a soln of a hydroxamic acid **2** (1.0 mmol) in THF (10 mL) at  $0\text{ }^\circ\text{C}$ , NMM (0.16 mL, 1.5 mmol) and T3P (0.89 mL, 1.5 mmol) were added and the mixture was stirred for 30 min. Then, the nucleophile (amine or alcohol, 1.5 mmol) was added and the mixture was refluxed for 3 h. The solvent was removed under reduced pressure, the residue was diluted with EtOAc (15 mL), and the organic layer was washed with 10% HCl (10 mL),  $\text{H}_2\text{O}$  (10 mL) and brine, then dried (anhyd  $\text{Na}_2\text{SO}_4$ ). The solvent was evaporated under reduced pressure to afford the product.

### S-Cyclohexyl Benzylthiocarbamate (3b)

Yield: 187 mg (75%); gum;  $R_f = 0.50$  ( $n\text{-hexane--EtOAc}$ , 7:3).

IR (KBr):  $1655\text{ cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 1.28\text{--}1.46$  (m, 6 H), 1.52–1.68 (m, 4 H), 4.36 (d,  $J = 6.2\text{ Hz}$ , 2 H), 5.98 (br, 1 H), 7.12–7.22 (m, 5 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 22.5$ , 31.1, 34.6, 46.7, 47.9, 125.6, 126.7, 127.5, 139.9, 166.7.

HRMS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{14}\text{H}_{19}\text{NOS}$ : 272.1085; found: 272.1091.

Anal. Calcd for  $\text{C}_{14}\text{H}_{19}\text{NOS}$ : C, 67.43; H, 7.68; N, 5.62. Found: C, 67.48; H, 7.71; N, 5.68.

### N-(Furan-2-yl)morpholine-4-carboxamide (3f)

Yield: 178 mg (91%); white solid; mp  $176\text{ }^\circ\text{C}$ ;  $R_f = 0.45$  ( $n\text{-hexane--EtOAc}$ , 7:3).

IR (KBr):  $1655\text{ cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 3.52$  (t,  $J = 7.2\text{ Hz}$ , 4 H), 3.72 (t,  $J = 7.6\text{ Hz}$ , 4 H), 6.85 (m, 1 H), 7.21 (d,  $J = 6.9\text{ Hz}$ , 1 H), 7.43 (d,  $J = 7.0\text{ Hz}$ , 1 H), 8.61 (br, 1 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 45.2$ , 66.7, 112.3, 116.8, 143.1, 145.9, 155.8.

HRMS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3$ : 219.0746; found: 219.0751.

Anal. Calcd for  $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3$ : C, 55.09; H, 6.16; N, 14.28. Found: C, 55.12; H, 6.13; N, 14.35.

### Benzyl Phenylcarbamate (3g)

Yield: 191 mg (84%); white solid; mp  $188\text{ }^\circ\text{C}$ ;  $R_f = 0.50$  ( $n\text{-hexane--EtOAc}$ , 7:3).

IR (KBr):  $1738\text{ cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 5.11$  (s, 2 H), 6.91 (br, 1 H), 7.21–7.65 (m, 10 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 66.4$ , 126.8, 127.1, 127.5, 129.1, 132.6, 133.4, 138.2, 143.1, 155.1.

ESI-MS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{14}\text{H}_{13}\text{NO}_2$ : 250.08; found: 250.09.

Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{NO}_2$ : C, 73.99; H, 5.77; N, 6.16. Found: C, 73.93; H, 5.81; N, 6.20.

### Benzyl 4-Bromophenylcarbamate (3h)

Yield: 242 mg (79%); pale yellow solid; mp  $167\text{ }^\circ\text{C}$ ;  $R_f = 0.45$  ( $n\text{-hexane--EtOAc}$ , 7:3).

IR (KBr):  $1742\text{ cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 5.12$  (s, 2 H), 6.31 (br, 1 H), 7.23–7.37 (m, 5 H), 7.53 (d,  $J = 8.2\text{ Hz}$ , 2 H), 7.78 (d,  $J = 8.4\text{ Hz}$ , 2 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 65.6$ , 121.3, 122.9, 127.2, 127.8, 128.9, 132.4, 134.9, 141.5, 155.9.

HRMS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{14}\text{H}_{12}\text{BrNO}_2$ : 327.9949; found: 327.9941.

Anal. Calcd for  $\text{C}_{14}\text{H}_{12}\text{BrNO}_2$ : C, 54.92; H, 3.95; N, 4.58. Found: C, 54.96; H, 3.88; N, 4.58.

### Ureidopeptides 5/Active Carbamates 6; General Procedure

To a soln of a N-protected amino acid hydroxamate **4** (1.0 mmol) in THF (10 mL) at  $0\text{ }^\circ\text{C}$ , NMM (0.16 mL, 1.5 mmol) and T3P (0.89 mL, 1.5 mmol) were added and the reaction mixture was stirred at  $0\text{ }^\circ\text{C}$  for 30 min. Then,  $\text{H}_2\text{N-Xaa-OMe}$  or a substituted phenol (1.2 mmol) was added and the reaction mixture was subjected to ultrasonication until completion (90 min, TLC analysis). Urea products which precipitated out from the reaction mixture were collected by filtration and recrystallized ( $\text{DMSO--H}_2\text{O}$ ). Otherwise, the urea or

carbamate products were isolated via the same simple workup as described in the general procedure for ureas/carbamates **3**.

**Methyl (S)-2-[[[(S)-1-(tert-butoxycarbonylamino)-2-phenylethyl]ureido]-3-methylbutanoate (Boc-Phe-ψ[NHCO]-Val-OMe, **5c**)**

Yield: 334 mg (85%); white solid; mp 138–139 °C;  $R_f$  = 0.50 (CHCl<sub>3</sub>–MeOH, 9:1).

IR (KBr): 1644, 1690, 1726 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 0.93 (d,  $J$  = 5.8 Hz, 6 H), 1.35 (s, 9 H), 1.8 (m, 1 H), 2.85 (d,  $J$  = 7.2 Hz, 2 H), 3.63 (s, 3 H), 3.83–3.93 (m, 2 H), 5.2 (br, 1 H), 6.35 (br, 1 H), 6.45 (d,  $J$  = 7.0 Hz, 1 H), 7.15–7.30 (m, 5 H).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 18.7, 19.5, 29.5, 37.1, 54.7, 57.5, 63.1, 78.2, 126.9, 127.6, 129.1, 137.9, 155.3, 156.9, 174.5.

HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>: 416.2161; found: 461.2169.

Anal. Calcd for C<sub>20</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>: C, 61.05; H, 7.94; N, 10.68. Found: C, 61.09; H, 7.98; N, 10.75.

**Methyl (S)-2-[[[(S)-4-Benzoyloxy-1-(tert-butoxycarbonylamino)-4-oxobutyl]ureido]-4-methylpentanoate {Boc-Glu(ONB)-ψ[NHCO]-Leu-OMe, **5d**}**

Yield: 379 mg (79%); white solid; mp 139 °C;  $R_f$  = 0.4 (CHCl<sub>3</sub>–MeOH, 9:1).

IR (KBr): 1656, 1702, 1742 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 0.91 (d,  $J$  = 4.8 Hz, 6 H), 1.32 (s, 9 H), 1.42 (m, 2 H), 1.65 (m, 1 H), 2.55 (m, 2 H), 2.92 (m, 2 H), 3.65 (s, 3 H), 3.81–3.92 (m, 2 H), 5.15 (s, 2 H), 5.33 (d,  $J$  = 4.7 Hz, 1 H), 6.35 (d,  $J$  = 6.4 Hz, 1 H), 6.54 (d,  $J$  = 5.8 Hz, 1 H), 7.3–7.4 (m, 5 H).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 22.1, 23.1, 24.7, 28.6, 37.9, 39.7, 41.9, 50.9, 61.9, 63.1, 78.7, 126.7, 127.6, 128.9, 137.7, 155.3, 156.8, 157.5, 178.1.

HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>24</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>: 502.2529; found: 502.2531.

Anal. Calcd for C<sub>24</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>: C, 60.11; H, 7.78; N, 8.76. Found: C, 60.18; H, 7.73; N, 8.74.

**2,4,5-Trichlorophenyl 1-[(9H-Fluoren-9-ylmethoxy)carbonylamino]-2-phenylethylcarbamate (Fmoc-Phe-ψ[NHCO]-OTcp, **6a**)**

Yield: 529 mg (91%); white solid; mp 142 °C;  $R_f$  = 0.35 (*n*-hexane–EtOAc, 7:3).

IR (KBr): 1695, 1742 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 2.85 (d,  $J$  = 6.2 Hz, 2 H), 3.81 (m, 1 H), 4.11 (t,  $J$  = 4.6 Hz, 1 H), 4.25 (d,  $J$  = 7.0 Hz, 2 H), 6.58 (br, 2 H), 7.23–8.15 (m, 15 H).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 38.9, 47.6, 52.5, 66.7, 120.0, 122.5, 124.6, 125.0, 127.1, 127.2, 127.8, 128.7, 129.1, 129.8, 132.0, 136.9, 141.2, 143.4, 151.4, 155.8, 156.6.

HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>30</sub>H<sub>23</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: 603.0621; found: 603.0626.

Anal. Calcd for C<sub>30</sub>H<sub>23</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 61.92; H, 3.98; N, 4.81. Found: C, 61.96; H, 3.95; N, 4.86.

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